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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,756	04/14/2006	Kenji Sasaki	P28062	5026

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
03/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/539,756	SASAKI ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/21/05, 4/14/06, 1/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1 and 5-18, in the reply filed on January 14, 2008 is acknowledged. The traversal is on the ground(s) that Unity of Invention rules do not contemplate search burden. This is not found persuasive because the restriction requirement mailed on December 12, 2007 set forth the lack of unity over Thompson, et al. (US PAT 5,130,418) as teaching the technical feature recited in claim 1, thus the technical feature is not special.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2-4, and 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 14, 2008.

3. Claims 1 and 5-18 are under examination.

Priority

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d), a certified English translation of

the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

The claims under examination receive the priority date of April 14, 2006 for art rejection purposes because the priority documents are in Japanese.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on October 21, 2005, April 14, 2006, and January 4, 2007 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 5-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite for reciting the phrase "substantially no influence" in claims 1, and 5-9. It is not clear what amount of activity is included in substantially no influence. For purposes of this art rejection the phase is being interpreted as “no influence”.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, and 5-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Kouno, et al. (US PG PUB 2005/0123532, published June 9, 2005).

The claims recite a method for protecting a thiol group in a protein having a free cysteine residue, which comprises adding a compound which has a disulfide bond in the molecule and exerts substantially no influence on the activity of the protein, wherein the compound which has a disulfide bond in the molecule and exerts substantially no influence on the activity of the protein is cystine, homocystine, lipoic acid or oxidized glutathione, wherein the protein is a recombinant protein, wherein the protein is an antibody, wherein the antibody is an F(ab')2 antibody, wherein the antibody is a monoclonal antibody, wherein the monoclonal antibody has a thiol group in its variable region, wherein the monoclonal antibody has a free cysteine residue in its variable region, wherein the monoclonal antibody comprises the amino acid sequences represented by SEQ ID NOs: 1, 2 and 3 in the Sequence Listing in its heavy chain hypervariable region, and the amino acid sequences represented by SEQ ID NOs: 4, 5 and 6 in the Sequence Listing in its light chain hypervariable region, wherein the

monoclonal antibody comprises a heavy chain variable region comprising the amino acid sequence represented by SEQ ID NO: 7 in the Sequence Listing and a light chain variable region containing the amino acid sequence represented by SEQ ID NO: 8 in the Sequence Listing, wherein the protein is produced by using a cell cultured in a serum-free medium. The claims also recite a method for protecting a thiol group in a protein having a free cysteine residue, which comprises adding a compound which has a disulfide bond in the molecule and exerts substantially no influence on the activity of the protein simultaneously or separately from a compound which has a thiol group in the molecule and exerts substantially no influence on the activity of the protein, wherein the compound which has a thiol group in the molecule and exerts substantially no influence on the activity of the protein is cysteine, homocysteine, glutathione or dihydrolipoic acid, wherein the compound which has a thiol group in the molecule and exerts substantially no influence on the activity of the protein is cysteine.

Kouno, et al. teach a method for producing a protein having a free cysteine in serum free medium. Kouno, et al. teach the method carried out in the presence of a reducing agent (cysteine) having capacity low enough not to reduce the disulfide linkage in the protein molecule but high enough to reduce the free cysteine, wherein the protein is a recombinant protein, wherein the protein is a monoclonal antibody, wherein the protein is the F(ab')2 fragment of the antibody. Kouno, et al. teach the use of a GAH antibody in the method. The GAH antibody has the CDR sequences of SEQ ID Nos. 1-6 of the instant application and the variable region sequences of SEQ ID Nos. 7 and 8 of the instant application (see sequence alignment). Kouno, et al. teach no deterioration

of the binding activity of the antibody after the steps of the method (example 12). Since the claims recite the same antibody as Kouno, et al. in the same method steps as Kouno, et al. all the limitations of the claims have been met.

10. Claims 1 and 5-11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunicki, et al. (Biochemistry, 1986. Vol. 25, pages 4979-4983, as cited on the IDS).

The claims have been described supra.

Kunicki, et al. teach generation of antibody Fab' fragments by pepsin digestion and reduction with L-cysteine which creates a free sulfhydryl group in the carboxy terminal region of the antibody fragment. The Fab' fragments generated by the method retained the ability to bind antigen. Since the active steps of the claimed method require addition of cysteine to an antibody which has no influence on the binding of the antibody, all the limitations of the claims have been met.

11. Claims 1 and 5-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson (US PAT 5,130,418 issued July 14, 1992, as cited in a previous office action).

The claims have been described supra.

Thompson teaches a method for treating recombinant bFGF protein with organic disulfides, specifically either glutathione disulfide or cysteine, which enhanced

stabilization of the protein molecule. Since the claims do not identify the specific protein of the method, all the limitations of the claims have been met.

12. Claims 1 and 5-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hosokawa, et al. (US PAT 5767246, issued June 16, 1998, as cited on the IDS).

The claims have been described supra.

Hosokawa, et al. teach preparation of a thiolated antibody by adding L-cysteine and polyethylene/glycol to a GAH antibody F'(ab)2 fragment. The GAH antibody has the same sequence as the instant antibody CDRs SEQ ID Nos. 1-6 and variable regions SEQ ID Nos. 7-8 (see sequence alignment). Hoskawa, et al. teach that the thiolated antibody retained the anti-cancer effect of the parent GAH antibody (figure 5). Since the claims contain the broad language of "comprises" in the method, the addition of polyethylene/glycol would be included in the instant method and all the limitations of the claims have been met.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1 and 7-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 10-17, and 19-25 of copending Application No. 10/497,516. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of the instant claims comprises adding a compound which has a disulfide bond to a protein wherein the compound is cysteine and the protein is an antibody having the CDR sequences of SEQ ID Nos. 1-6 and the variable region sequences of SEQ ID Nos. 7-8.

The method of 10/497,516 comprises adding a reducing agent to a protein in the presence of ascorbic acid and sodium chloride or potassium chloride wherein the reducing agent is cysteine and the protein is an antibody that is identical to the antibody of the instant claims (see sequence alignment for 102(a) above). Since the instant claims require adding cysteine to an antibody molecule and the 10/497,516 claims add cysteine to the same antibody molecule, the instant claims are anticipated by the claims of 10/497,516.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

March 13, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643